



Indion 190 resin: Reusable catalyst for the synthesis of quinoxalines and pyrido-pyrazines at ambient temperature

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ABSTRACT

An efficient method for synthesis of quinoxalines and substituted pyrido-pyrazines has been developed from different 1,2-dicarbonyl compounds and substituted 1,2-diamines using Indion 190 resin as a solid acid catalyst. Ambient reaction conditions, high product yield and reusability of the catalyst with minimal loading are the salient features of the present protocol.

1. Introduction

Quinoxaline is a privileged ring system and its derivatives represent an important class of nitrogen containing heterocycles as they constitute useful dyes and intermediates in organic synthesis [1]. As depicted in literature, pyrido[2,3-b]pyrazines and pyrido[3,4-b]pyrazines are exhibiting promising biological properties and are used for the treatment of malignant tumors and other diseases related to cell proliferations. Functionalized quinoxalines exhibit broad biological activities and have been evaluated as anticancer [2], antiviral [3], antibacterial [4], and kinase inhibition agents [5,6]. In addition to their therapeutic properties, quinoxalines have also found applications as dyes [7], organic semiconductors [8] and chemically controllable switches [9]. Consequently, there has been tremendous interest in developing efficient synthetic strategies for preparing quinoxalines due to their widespread applications in the fields of medicinal, industrial and synthetic organic chemistry. Commonly employed method involves condensation of an aryl-1,2-diamine with a 1,2-dicarbonyl in refluxing ethanol or acetic acid for 2-12 h yielding 34-85% of product [10]. Several improved methods reported in the literature for the synthesis of quinoxalines include microwave synthesis [11], the use of PEG-400 [12], RuCl₂(PPh₃)₃-TEMPO [13], CAN [14], CuSO₄·5H₂O [15], SA/MeOH [16], montmorillonite K-10 [17], InCl₃ [18], Zn/proline [19], Ga(OTf)₃ [20], HClO₄-SiO₂ [21], β-cyclodextrins in water [22], FeMAP [23], TiO₂-P25 [24], ZnO-beta zeolite [25], silica-supported antimony(III) chloride [26] as catalysts.

Indion 190 resin, a macroporous strongly acidic cation exchanger with styrene DVB matrix, is used as a heterogeneous catalyst in modern organic synthesis [27,28]. It is a sulphonic acid resin with an exchange capacity of 4.7 meq/g. Particle size

of the catalyst ranges from 0.42 to 1.20 mm and maximum operating temperature is 150 °C. Venturing towards the development of efficient and environmentally benign synthetic strategies, we have investigated the synthesis of substituted quinoxalines and pyrido-pyrazines by condensation of 1,2-diamines and 1,2-diketones using Indion-190 resin, an efficient reusable catalyst, at room temperature (Scheme 1).

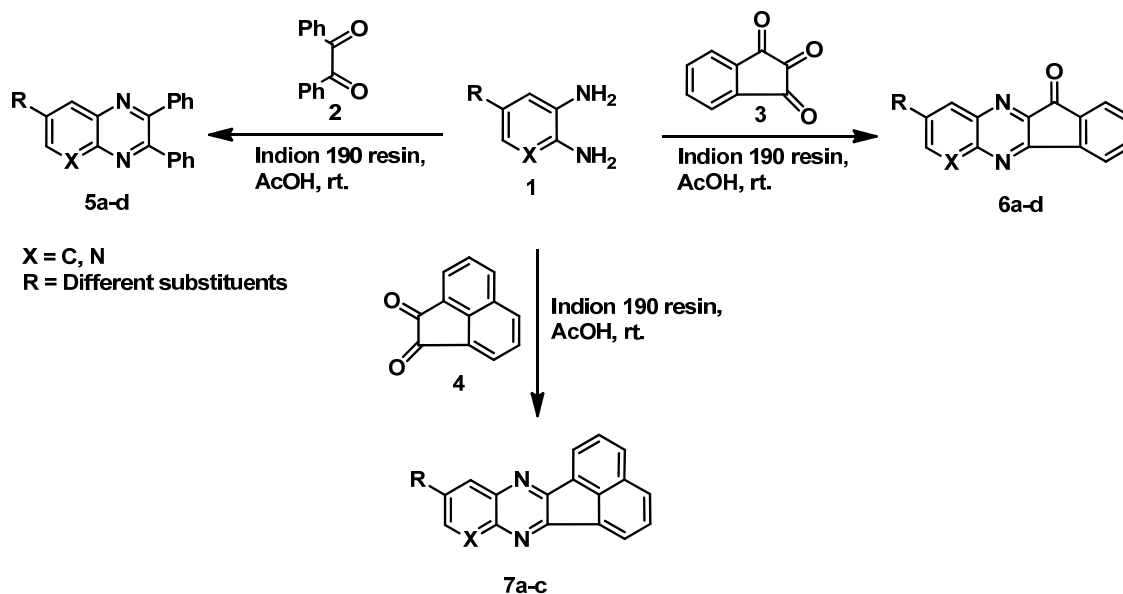
2. Experimental

2.1. Instrumentation

The reactions and purity of quinoxalines were monitored by thin layer chromatography (TLC) using glass plates coated with silica gel. The isolated products (**5d**, **6a-d** and **7a-c**) were purified by column chromatography whereas (**5a-c**) were purified by recrystallization. ¹H NMR and ¹³C NMR spectra were recorded on Bruker Avance Spectrospin 300 MHz. All NMR samples were run in CDCl₃ and chemical shifts are expressed as δ relative to internal TMS. IR spectra were obtained on Perkin Elmer FT-IR spectrophotometer spectrum 2000 using potassium bromide pellets. Mass spectra were obtained on Thermo-Finnigan Discovery-Max GC-MS. All the melting points were determined in an open capillary tube using Expo Hi Tech. melting point apparatus.

2.2. Typical procedure

To a mixture of 1,2-diamine (**1**) (1 mmol) and benzil (**2**) or ninhydrin (**3**) or acenaphthenequinone (**4**) (1 mmol) in AcOH (5 mL), Indion 190 resin (20%/w) with respect to 1,2-diamine was added and the mixture was stirred at room temperature. The progress of reaction was monitored using thin layer chromatography.



Scheme 1

After completion of reaction, catalyst was filtered and solvent was distilled out. The reaction mass was poured in ice cold water and filtered to afford crude product. The isolated products (5a-5c) were purified by recrystallization with 95% ethanol whereas (5d, 6a-d and 7a-c) were purified by column chromatography.

3. Results and discussion

Initially, a model condensation reaction between 1,2-phenylenediamine and benzil was subjected to varying reaction conditions. In order to determine the optimum conditions, we first examined the effective catalyst concentration (Table 1) followed by the influence of solvent (Table 2). We also analyzed the reusability of the sulphonic acid resin catalyst (Figure 1). For a typical experiment, 1,2-phenylenediamine and benzil were stirred in AcOH (5 mL) at room temperature in presence of Indion 190 resin (20 %/w). Reaction was completed in 10 min to afford 2,3-diphenyl quinoxaline (Table 3, Entry 5a, 97%). Encouraged by the outstanding results obtained from the present protocol and to check its further versatility and scope, we have employed various 1,2-diamines and 1,2-dicarbonyls, the results of which are summarized in Table 3.

Table 1. Optimization of the amount of Indion 190 resin ^a.

Entry	Catalyst concentration (%/w)	Yield (%) ^b
1	10	81
2	20	97
3	30	92
4	40	92
5	50	92
6	60	64

^a Reaction condition: 1,2-phenylenediamine (1 mmol), benzil (1 mmol), room temperature and AcOH (5 mL).

^b Isolated yield.

3.1. Optimization of catalyst

Catalyst concentration plays a vital role in synthesis of quinoxalines. Application of 20%/w of Indion 190 resin gave excellent yield of 2,3-diphenyl-quinoxaline (Table 1). At a higher amount of catalyst, the yield of the corresponding product decreases may be due to increase in the acidity of the reaction medium.

Table 2. Effect of solvents ^a.

Entry	Solvent	Time (min)	Yield (%) ^b
1	MeOH	30	94
2	EtOH	75	85
3	MeCN	75	83
4	MeOH:H ₂ O(1:1)	120	90
5	EtOH:H ₂ O(1:1)	120	88
6	MeCN:H ₂ O(1:1)	160	86
7	AcOH ^c	10	97

^a Reaction condition: 1,2-phenylenediamine (1 mmol), benzil (1 mmol), catalyst Indion 190 resin (20% w/w), room temperature and solvent (5 mL).

^b Isolated yield.

^c Glacial acetic acid AR grade with less than 0.98 % moisture content was used.

Table 3. Synthesis of quinoxalines and pyrido-pyrazines ^a.

Entry	R	X	Product	Time (min)	Yield (%) ^b
1	H	C	5a	10	97
2	NO ₂	C	5b	15	92
3	CH ₃	C	5c	10	94
4	Br	N	5d	20	90
5	H	C	6a	20	92
6	NO ₂	C	6b	35	83
7	CH ₃	C	6c	30	89
8	Br	N	6d	25	84
9	H	C	7a	25	93
10	NO ₂	C	7b	25	87
11	Br	N	7c	30	85

^a Reaction condition: 1,2-diamines (1 mmol), 1,2-diketones (1 mmol), catalyst: Indion 190 resin (20% w/w), solvent: AcOH (5 mL), room temperature.

^b Isolated yield.

3.2 Effect of solvent on preparation of quinoxaline

In order to elucidate the role of the solvents, various solvents were used to evaluate the scope and limitations of the reaction. Solvent optimization study revealed that, glacial acetic acid was the most conducive solvent favoring quinoxaline ring formation (Table 2).

3.3. Recycling of Indion-190 resin

The reusability of the catalyst is important for the large-scale operation and from an industrial point of view. Therefore, the recovery and reusability of Indion 190 resin was examined. The catalyst was separated and reused after washing with ethanol and drying at 110 °C. Figure 1 illustrates, the catalyst

can be used four times with consistent yield. The color of the catalyst remains the same even after the four cycles.

In the present synthesis, the activation of the carbonyl oxygen by the acidic proton of Indion 190 resin followed by cyclocondensation with aryl diamine and subsequent loss of water molecule results in the product formation. A variety of quinoxalines and pyrido-pyrazines (Table 3) have been synthesized in good yields ranging from 97 to 83% irrespective of the complexities and different substituted functionalities. All the synthesized products are known and reported in the literature [11,29,30].

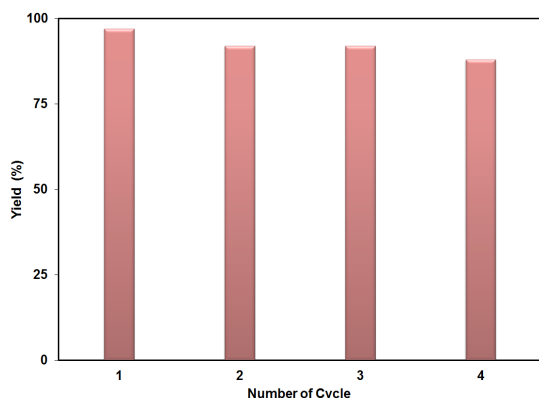


Figure 1. Recyclability of the catalyst.

4. Conclusion

In conclusion, commercially available Indion-190 resin, an inexpensive, non-toxic and highly reusable catalyst provides an environmentally benign route for easy access to a variety of quinoxaline and pyrido-pyrazine derivatives. An efficient and highly reusable catalytic system, mild reaction conditions, and short reaction time with high product yield make the present protocol more attractive for practical purposes.

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